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| APPLICATION NO. | FILING DATE | FIRST NAMED INVENTOR | ATTORNEY DOCKET NO. | CONFIRMATION NO. |
|-----------------|-------------|----------------------|---------------------|------------------|
| 10/726,680 | 12/04/2003 | Dan Peters | 2815-0253P | 5690 |

2292 7590 02/22/2005

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EXAMINER

HUANG, EVELYN MEI

ART UNIT PAPER NUMBER

1625

DATE MAILED: 02/22/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

| | | | |
|------------------------------|--------------------------------------|--------------------------------------|--|
| Office Action Summary | Application No. 10/726,680 | Applicant(s) PETERS ET AL. | |
| | Examiner Evelyn Huang | Art Unit 1625 | |

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on 30 November 2004.
- 2a) ☐ This action is **FINAL**. 2b) ☒ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 1,8,10-13,26-35,38 and 39 is/are pending in the application.
- 4a) Of the above claim(s) 8,10,12 and 38 is/are withdrawn from consideration.
- 5) ☐ Claim(s) _____ is/are allowed.
- 6) ☒ Claim(s) 1,11,13 and 26-35 is/are rejected.
- 7) ☒ Claim(s) 39 is/are objected to.
- 8) ☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on _____ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

- 12) ☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☒ All b) ☐ Some * c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
 2. ☒ Certified copies of the priority documents have been received in Application No. 09/864,367.
 3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

- | | |
|---|---|
| 1) <input checked="" type="checkbox"/> Notice of References Cited (PTO-892) | 4) <input type="checkbox"/> Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ |
| 2) <input type="checkbox"/> Notice of Draftsperson's Patent Drawing Review (PTO-948) | 5) <input type="checkbox"/> Notice of Informal Patent Application (PTO-152) |
| 3) <input checked="" type="checkbox"/> Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____ | 6) <input type="checkbox"/> Other: _____ |

DETAILED ACTION

1. Claims 1, 8, 10-13, 26-35, 38-39 are pending.

Election/Restrictions

2. In response to the restriction requirement mailed on 9-3-2004, Applicant has elected with traverse the compound of Group III, claims 11, 39 and claims 1, 13 and 26 in part.

Applicants argue that unity of invention exist because Group I-III compounds share a substantial common core and have the same utility as modulator of nicotinic acetylcholine receptor.

On the contrary, compounds of Group II has been shown to have insecticidal, acaricidally or nematocidal activity (Godfrey, WO 98/46600, PTO-1449), while the compound of Group III has been shown to be inhibitors of serotonin reuptake (Audia, 6107307, PTO-1449). A compound of Group III has been shown to be an intermediate in the process of making a biphenylamide derivative having 5HT_{1D} antagonizing activity (Gaster, 5919932, column 8, Description 7).

Should applicant traverse on the ground that these groups of inventions are not patentably distinct, applicant should submit evidence or identify such evidence now of record showing these compounds to be obvious variants or clearly admit on the record that this is the case. In either instance, if the examiner finds one of the inventions unpatentable over the prior art, the evidence or admission may be used in a rejection under 35 U.S.C. 103(a) of the other invention.

Applicants have requested rejoining the method claims 27-35 with the Group III invention. Accordingly, Group IV, claims 27-35 have been rejoined.

Claim Rejections - 35 USC § 112

3. The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

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Claims 1, 11, 13, 26-35 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

- a. Claim 1, the meaning of the term 'general' in 'general formula' is unclear, its deletion is recommended.
- b. A broad range or limitation together with a narrow range or limitation that falls within the broad range or limitation (in the same claim) is considered indefinite, since the resulting claim does not clearly set forth the metes and bounds of the patent protection desired. In the present instance, claim 27 recites the broad recitation 'a living body', and the claim also recites 'including human' which is the narrower statement of the range/limitation. Deletion of 'including human' is recommended.
- c. Claim 28, the term 'related' in 'related to smooth muscle contraction.....related to neuro-degeneration....related to inflammation' is open-ended since it is unclear what is considered to be 'related' in the absence of a full definition of the term.
- d. Claims 33, 35, it is recommended that 'such as' be replaced with 'from the group selected from' to better define the claim.

The rejection is applicable to claims dependent on the above claims.

Claim Rejections - 35 USC § 112

4. The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 27, 28 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

The instant method of treatment or alleviation of a disease responsive to the activity of a nicotinic acetylcholine receptor modulator as recited in claim 27 reaches out to as yet unidentified diseases/conditions responsive to the activity of a nicotinic acetylcholine receptor modulator, a description of which is not found in the specification.

The instant method of claim 28 reaches out to as yet unidentified diseases/conditions of the CNS, the diseases/disorders caused by or related to smooth muscle contraction, an endocrine disorder, neurodegeneration, inflammation, pain etc etc, a description of which is not found in the specification.

Claim Rejections - 35 USC § 112

5. The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 27-35 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention. ***.

a. *Nature of the invention.*

The instant invention is drawn to an azabicyclo-[3.2.1] octane or octene compound for use as a modulator of nicotinic acetylcholine receptor in the treatment or alleviation of a disease responsive to the activity of a nicotinic acetylcholine receptor modulator. The diseases are recited on pages 19-20 of the specification..

b. *State of the prior art and the level of the skilled in the art.*

Different subclasses, including the $\alpha 7$ nicotinic acetylcholine receptor, have been shown to exist. Agonists and antagonists of nicotinic receptors are known (Holladay et al. J. Med. Chem. 1997, 40:4169-4188; page 4171, Table 1). The exact role of $\alpha 7$ nicotinic acetylcholine receptor is still under investigation and has not been fully established (page 4173, column 1).

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3-substituted azabicyclo-[3.2.1] octene compounds similar to the instant are known to be inhibitors of monoamine reuptake (Moldt, WO 97/13770, PTO-1449).

It is well recognized in the art that affinities for nicotinic receptors do not differentiate agonists from antagonists, which are known to elicit different effects on disease conditions mediated by the nicotinic receptors. For example, nicotinic antagonists such as mecamylamine impair working memory function, while nicotinic agonist treatment may improve attention, learning and memory and nicotinic antagonist treatment can cause deficits (Levin, Psychopharmacology 1998, 138(3-4): 217-30). At present, the correlation between receptor binding of the ligand and its effect on the various diseases in vivo has not been established.

Furthermore, at the time of the invention, there is no umbrella drug known for treatment or alleviation of all the conflicting and opposing conditions/disorders/diseases/disorders of the CNS, diseases/disorders caused by or related to smooth muscle contraction, an endocrine disorder, neurodegeneration, inflammation, pain etc etc.

The level of the skilled in the nicotinic acetylcholine receptor art is high.

c. *Predictability/unpredictability in the art.*

The high degree of unpredictability is well recognized in the nicotinic acetylcholine receptor art. A slight modification of the compound would lead to profound changes in its biological activity as evidenced in the very different affinities exhibited by structurally similar compounds (reviewed by Holladay on page 4183). One of ordinary skill in the art therefore would have no basis to extrapolate the results to compounds structurally removed from the tested compounds.

d. *Amount of guidance/working examples.*

The preparation of the example compounds has been described.

The procedures for the in vitro nicotinic acetylcholine receptor binding assays are described in Example 2. The results have not been shown. No functional assays or in vivo procedures are described.

e. *The breadth of the claims.*

Applicant's assertion that all the inventive compounds are effective modulators (i.e. agonists, antagonists, partial agonists and allosteric modulators as defined on page 5 of the specification) useful for treatment or alleviation of any disease responsive to the activity of a

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nicotinic acetylcholine receptor modulator (including the conflicting and opposing conditions/ disease/disorder of the CNS, diseases/disorders caused by or related to smooth muscle contraction, an endocrine disorder, neurodegeneration, inflammation, pain etc, and the as yet unidentified diseases/conditions whose description is not found in the specification) does not commensurate with the scope of the objective enablement, especially in view of the high degree of unpredictability in the art, the lack of correlation between in vitro receptor binding and the effect on the diseases in a human or an animal, and the absence of guidance as to which compounds are agonists, antagonists, partial agonists or allosteric modulators (paragraphs c, d above).

f. *Amount of undue experimentation.*

Since insufficient teaching and guidance are provided by the specification (paragraphs c-d above), one of ordinary skill in the art, even with high degree of skill, would not be able to use the compounds as claimed without undue experimentation.

Claim Rejections - 35 USC § 102

6. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless –

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 1, 11 are rejected under 35 U.S.C. 102(b) as being anticipated by Gaster (5919932). The compound of Description 7 (column 8) is encompassed by the instant claims.

Allowable Subject Matter

7. Claim 39 is objected to as being dependent upon a rejected base claim, but would be allowable if rewritten in independent form including all of the limitations of the base claim and any intervening claims.

The 3-[7-quinolinyl]-8-methyl-8-azabicyclo[3.2.1]oct-ene of instant claim 39 is an octane whereas the compound of Description 7 of Gaster (5919932) is an octane, and furthermore, it

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does not have the 6-methoxy as recited in Gaster's compound. Motivation to modify Gaster's compound via multiple changes to arrive at the instant invention is lacking.

The compounds of Audia (6107307, PTO-1449; column 15, Examples 1-2; columns 17-19, Examples 8-12) have the bicyclic heterocyclic ring attached to the azabicyclic [3.2.1]octene via the hetero ring of the bicyclo, whereas the bicyclic heterocyclic ring is attached to the azabicyclic [3.2.1]octene via the benzene ring of the bicyclo in the instant compounds. Lacking is the motivation to modify Audia's compounds to arrive at the instant invention.

8. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Evelyn Huang whose telephone number is 571-272-0686. The examiner can normally be reached on Tuesday-Friday.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Cecilia Tsang can be reached on 571-272-0562. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).


Evelyn Huang
Primary Examiner
Art Unit 1625